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Ugi/Smiles access to pyrazine scaffolds

Anaelle Barthelon, Aurélie Dos Santos, Laurent El Kaïm *, Laurence Grimaud *

Laboratoire Chimie et Procédés, DCSO, UMR 7652, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, Paris 75015, France

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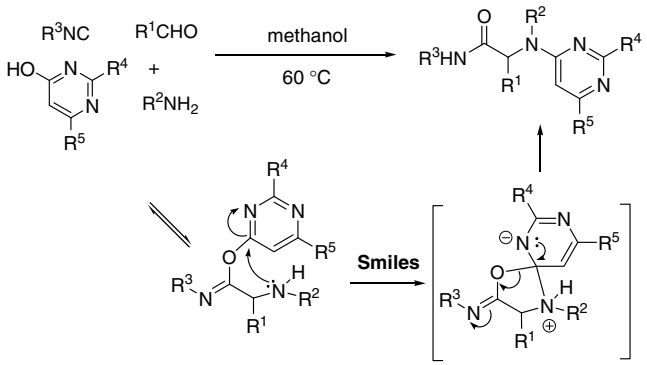
Abstract

New pyrazine and quinoxaline scaffolds were obtained via an Ugi/Smiles four-component coupling of pyrazinone or quinoxalinone derivatives with isocyanides, aldehydes, and primary amines.

A few years ago, we reported a new Ugi-type four-component coupling of isocyanides with aldehydes, primary amines, and electron-deficient phenols.[1] The key step of this transformation involves a Smiles rearrangement of a phenol imidate intermediate. We also showed that the scope of this reaction could be extended to the use of activated pyridines as well as hydroxy- and mercapto-pyrimidines (Scheme 1).[2] Now we report the results of our study on pyrazinones and their benzo-fused analogues, quinoxalinones.



Scheme 1.

Pyrazines represent an important class of heterocyclic compounds.[3] As several biosynthetic paths allow the conversion of an amino acid into a pyrazine, this structural unit is found in many natural products. They are important flavor ingredients in food,[4] and have shown interesting anticancer[5] as well as antituberculosis[6] activities. Pyrazines have been used widely as agrochemicals as well.[7] These properties prompted us to examine the potential of the Ugi–Smiles coupling for the preparation of aminopiperazine libraries and their benzo-fused analogues, quinoxalines.

Different pyrazinones were prepared by condensing α-dicarbonyl compounds with the corresponding α-amino amides. These pyrazinones were treated with a stoichiometric amount of a carbonyl compound, an amine and an isocyanide to perform the Ugi–Smiles coupling. The expected amino-substituted pyrazines were obtained in moderate to good yields as shown in Table 1.[8] The best yields were obtained in toluene at 100 °C. Under these conditions, *tert*-butylisocyanide gave a poor yield of product due to its low boiling point (Table 1, entry 4). The dimethylpyrazine derivatives **1d–f** reacted sluggishly and gave low yields of the desired adducts (Table 1, entries 9–11).

Next, quinoxalinones were investigated as potential partners in this four-component coupling. Due to the poor solubility of quinoxalinone **3**, toluene had to be replaced by DMSO as a solvent.[9] Under these conditions, the desired adducts were obtained albeit in poor yields (Scheme 2).

Afterwards, we envisioned the use of mercapto derivatives to improve the efficiency of these couplings. Indeed,

* Corresponding authors. Tel.: +33 145525537; fax: +33 145528322 (L.E.K.).
E-mail addresses: laurent.elkaim@ensta.fr (L. E. Kaïm), laurence.grimaud@ensta.fr (L. Grimaud).

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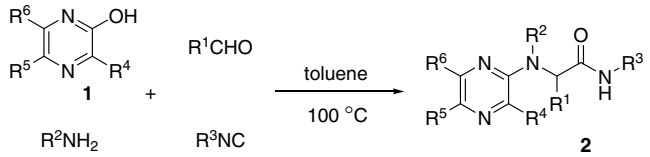
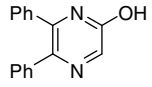
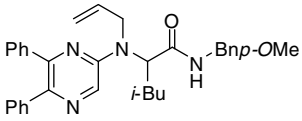
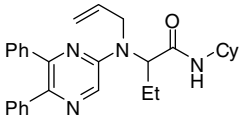
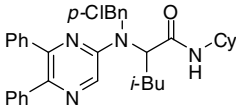
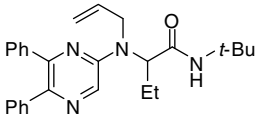
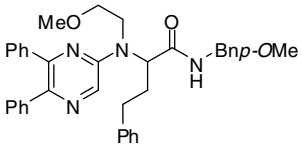
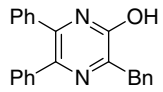
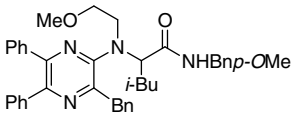
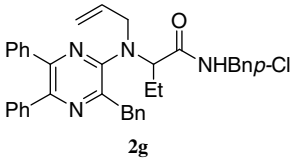
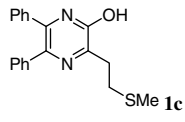
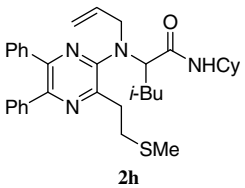
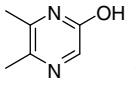
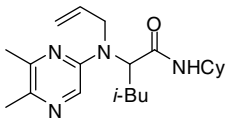
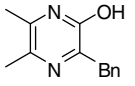
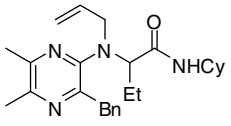
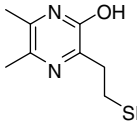
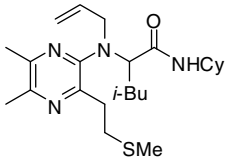
Table 1
Four-component formation of amino-pyrazines

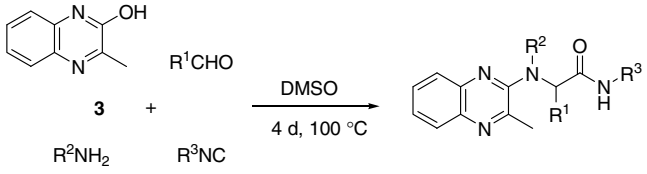


Entry	Pyrazinone	Time	Product	Yield (%)
1	 **1a**	12 h	 **2a**	92
2	**1a**	12 h	 **2b**	59
3	**1a**	12 h	 **2c**	93
4	**1a**	12 h	 **2d**	31
5	**1a**	12 h	 **2e**	76
6	 **1b**	6 d	 **2f**	73
7	**1b**	4 d	 **2g**	29
8	 **1c**	2 d	 **2h**	43

(*continued on next page*)

Table 1 (*continued*)

Entry	Pyrazinone	Time	Product	Yield (%)
9	 **1d**	3 d	 **2i**	45
10	 **1e**	2 d	 **2j**	15
11	 **1f**	2 d	 **2k**	11



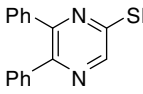
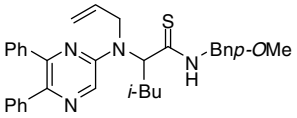
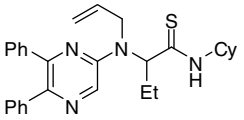
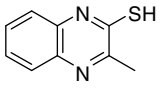
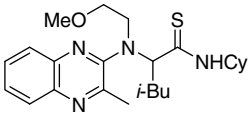
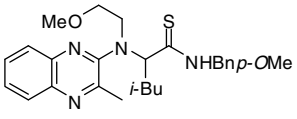
R^1	R^2	R^3	Yield (%)
i-Bu	CH_2CH_2OMe	Cy	16
i-Bu	All	Cy	8
Et	All	*p*-MeOBn	9

Scheme 2.

previous work on pyrimidines and benzo-fused heterocycles, such as benzothiazoles and benzoxazoles, demonstrated a higher reactivity of mercaptans over the corresponding hydroxy derivatives.[10] Mercaptopyrazinones and quinoxalinones were obtained by the treatment of the corresponding hydroxy derivatives with P_2S_5. When submitted to the Ugi–Smiles coupling, these mercaptans turned out to be less efficient than the corresponding hydroxyl derivatives (Table 2).[11] The higher solubility of quinoxaline **4b** allowed the reaction to be performed in toluene, however the yields were not improved.

To conclude, we have disclosed a new multicomponent formation of aminopyrazines by an Ugi-type procedure. The access to these new scaffolds confirms further the utility of Ugi–Smiles couplings for the preparation of amino-substituted nitrogen heterocycles. The extension of these couplings to triazines and tetrazines as well as our efforts to improve these additions with Lewis acids will be reported in due course.

Table 2
Thioamide formation from a mercaptopyrazinone and a mercapto-quinoxalinone

Entry	Mercapto derivative	Time (h)	Product	Yield (%)
1	 **4a**	12	 **5a**	76
2	**4a**	12	 **5b**	36
3	 **4b**	12	 **5c**	31
4	**4b**	12	 **5d**	9

Acknowledgments

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8. *Typical procedure for* **2a**: To a solution of 198 mg (0.8 mmol, 1 equiv) of 5,6-diphenylpyrazin-2-ol **1a** in 1 mL of toluene were added 60 μL of allylamine (0.8 mmol, 1 equiv), 88 μL of isobutyraldehyde (0.8 mmol, 1 equiv), and 120 μL of *para*-methoxybenzylisonitrile (0.8 mmol, 1 equiv). The resulting mixture was stirred at 110 °C for 12 h. The solvent was then removed in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/AcOEt: 95:5) to give 383 mg (92%) of **2a** as a white solid. Mp 116–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.36–7.23 (m, 10H), 6.96 (d, $J = 8.6$ Hz, 2H), 6.83 (t, $J = 5.3$ Hz, 1H), 6.71 (d, $J = 8.6$ Hz, 2H), 5.87 (ddt, $J = 15.6$, 10.4, 5.1 Hz, 1H), 5.42 (t, $J = 7.1$ Hz, 1H), 5.30 (dd, $J = 17.2$, 10.6 Hz, 2H), 4.29–4.28 (m, 2H), 4.23–4.21 (m, 1H), 4.10–4.06 (m, 1H), 3.76 (s, 3H), 2.02–1.95 (m, 1H), 1.84–1.77 (m, 1H), 1.69–1.62 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.8, 159.2, 152.2, 148.8, 141.5, 139.4, 139.3, 134.1, 130.4, 129.9, 129.8, 129.7, 129.2, 128.7, 128.5, 128.5, 127.8, 118.0, 114.4, 56.1, 55.6, 48.1, 43.3, 37.7, 25.3, 22.9. HRMS: calcd for $C_{33}H_{36}N_4O_2$ 520.2838. Found 520.2839.
9. The reaction was performed as well in MeOH, CH_3CN and in a 10:1 mixture of toluene:water without any improvement in the yield.
10. El Kaïm, L.; Gizolme, M.; Grimaud, L. *Synlett* **2007**, 465.
11. *Typical procedure for* **5b**: To a solution of 264 mg (1 mmol, 1 equiv) of 5,6-diphenylpyrazine-2-thiol **4a** in 1 mL of toluene were added 75 μL of allylamine (1 mmol, 1 equiv), 108 μL of propanal (1 mmol, 1 equiv), and 110 μL of cyclohexylisonitrile (1 mmol, 1 equiv). The resulting mixture was stirred at 110 °C for 3 days. The solvent was then removed in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/petroleum ether: 60:40) to give 169 mg (36%) of **5b** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 8.13 (s, 1H), 7.40–7.26 (m, 10H), 5.96–5.87 (m, 1H), 5.33–5.27 (m, 2H), 5.08 (br s, 1H), 4.52 (dd, $J = 18.2$, 4.8 Hz, 1H), 4.20–4.07 (m, 2H), 2.47–2.37 (m, 1H), 2.15–2.04 (m, 1H) 1.78–1.60 (m, 2H), 1.43–1.27 (m, 3H), 1.20–1.10 (m, 2H) 1.00 (dd, $J = 7.6$, 7.0 Hz, 3H), 0.86–0.77 (m, 1H), 0.70–0.60 (m, 1H), 0.52–0.43 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.5, 152.1, 148.1, 141.4, 139.8, 138.9, 134.3, 130.5, 129.9, 129.8, 129.0, 128.8, 128.5, 127.9, 117.7, 67.3, 53.6, 49.0, 31.3, 30.8, 25.4, 24.8, 24.4, 11.7. HRMS: calcd for $C_{29}H_{34}N_4S$ 470.2504. Found 470.2509.